REMARKS

The Applicants would like to thank the Examiner for the telephone interview of October 2, 2002. A figure prepared by the Applicants' representative describing the present invention is attached herewith and a summary of the issues discussed during the interview follows.

Upon entry of this Amendment, claims 23 to 32 will be pending in this application, of which claims 23 and 24 are independent. Claims 14 to 22 were cancelled and replaced with claims 23 to 32. Support for the new claims can be found throughout the specification as filed. Therefore, no new matter has been added as a result of this Amendment and the Applicants respectfully request reconsideration and allowance of the present application.

Claims 14 to 22 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for allegedly containing grammatical and idiomatic errors. These claims have been cancelled and replaced with claims that conform to current U.S. practice. Consequently, the Applicants respectfully request removal of this rejection.

Claims 14 to 22 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Bergmann *et al.* (U.S. Pat. No. 5,814,461) and/or Morris *et al.* (*J. Biol. Chem.* 268(15), 10900 – 10905, 1993) in view of Morgenthaler *et al.* (*J. Clin. Endocrinol. Metab.* 81(2), 700 – 706, 1996). The Applicants respectfully disagree for at least the following reasons.

The pending claims recite a method for the determination of TSH receptor autoantibodies by using immobilized recombinant human TSH receptors. In Bergmann *et al.*, TSH receptor autoantibodies are detected by a method using immobilized TSH antibodies. In Morris *et al.*, peptides comprising the sequence of the extracellular domain of the human TSH receptor were synthesized and their interaction with TSH was measured by the inhibition of labeled TSH to native TSH receptors. Neither the TSH nor the TSH receptor were immobilized in Morris *et al.* Morgenthaler *et al.* studied the binding of TSH receptor autoantibodies to human TSH receptor. The TSH receptor is not immobilized in Morgenthaler *et al.*

In order to establish a *prima facie* case of obviousness, three basic conditions must be met. First, there must be some suggestion or motivation to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the combination of references must teach or suggest all the claim limitations (MPEP §2143).

A person of ordinary skill in the art would not have had a reasonable expectation of success in combining Bergmann *et al.* with Morgenthaler *et al.* because merely replacing an immobilized TSH with an immobilized TSH receptor is a fundamental change in the assay. For an assay using an immobilized TSH receptor to be effective, the immobilized TSH receptor has to be functional, i.e., able to bind TSH receptor autoantibodies. The Examiner has not provided any references to show how an immobilized TSH receptor could have been made functional. Indeed, the immobilization of a functional TSH receptor was not possible prior to the present invention (see page 4, lines 20 to 24 in the specification as filed).

Not only is there is no motivation to combine Morris *et al.* with Morgenthaler *et al.*, but even if one skilled in the art were to effect this combination, it still would not teach or suggest all the claim limitations of the present invention. In particular, there is no indication in either Morris *et al.* or Morgenthaler *et al.* of any peptide being immobilized. All the experiments of Morris *et al.* and Morgenthaler *et al.* are conducted in solution.

The Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness and that this application is in condition for allowance. Therefore, the Applicants respectfully request a timely Notice to that effect. Should questions relating to patentability remain, the Examiner is invited to contact the undersigned to discuss the same.

Respectfully submitted,

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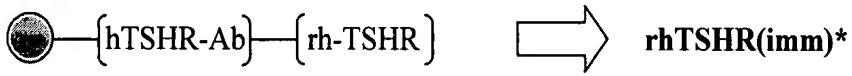
- The substance detected in both the present invention and in Bergmann *et al.* is the TSH receptor auto antibody (i.e., TSHR-auto-Ab)
- The structure immobilized in the present invention is the TSH receptor (i.e., TSHR)
- The structure immobilized in Bergmann *et al.* is the antibody against the hormone (i.e., TSH-Ab)

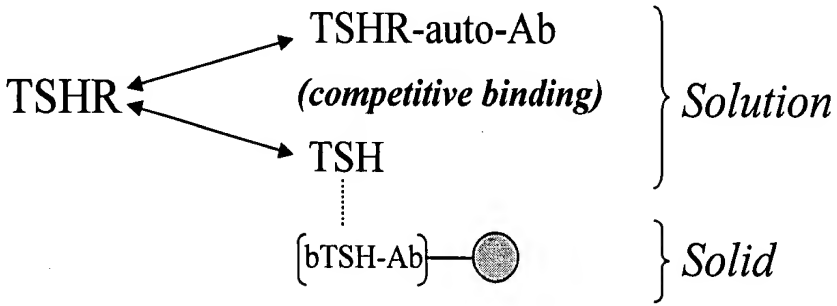
Present Invention:

rhTSHR(imm)* = immobilized and purified recombinant human TSH Receptor, i.e.,



- First step: rhTSHR(imm)* binds to TSHR-auto-Ab (TSH receptor auto antibody)
- Second step: Any rhTSHR(imm)* **not** bound to TSHR-auto-Ab binds to ^{125}I-bTSH (labelled bovine TSH)
- The amount of TSHR-auto-Ab can be determined by subtracting bound ^{125}I-bTSH (which can be quantified) from total amount of rhTSHR(imm)*
- The first and second steps can be conducted simultaneously.

Bergmann *et al.*:



Application Serial No: 09/381,032
Examiner: P.N. Huynh